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INTELLECTUAL PROPERTY **INDIA**

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH
W - 5, WEST PATEL NAGAR
NEW DELHI - 110 008.

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application, Provisional Specification*** *and* ***Drawing Sheets*** *filed in connection with Application for Patent No.****1004/Del/2003*** *dated* ***14th August 2003.***

Witness my hand this 10th day of September 2004.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

Chemical

1004-DEL-03

C07D501/04
C07D501/12
C07D501/24

FORM 1

THE PATENTS ACT, 1970

(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 5(2), 7, 54 and 135; and rule 39)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"AN EFFICIENT PROCESS FOR SELECTIVE PREPARATION OF Z-ISOMER OF CEFDITOREN AND PHARMACEUTICALLY ACCEPTABLE SALTS AND ESTERS THEREOF"**

(b) that the Provisional Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. YATENDRA KUMAR
b. MOHAN PRASAD
c. KAPTAN SINGH
d. ASHOK PRASAD
e. SANTOSH RICHHARIYA

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows: **NOT APPLICABLE**

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: **NOT APPLICABLE**

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on ..... Under section 16 of the Act. **NOT APPLICABLE**

7. That we are the assignee or legal representatives of the true and first inventors.

8. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana). INDIA.

9. Following declaration was given by the inventors or applicants in the convention country:
We. YATENDRA KUMAR, MOHAN PRASAD, KAPTAN SINGH, ASHOK PRASAD, SANTOSH RICHHARIYA of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention or applicant in the convention country declare that the applicant herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a.

(YATENDRA KUMAR)

b.

(MOHAN PRASAD)

c.

(KAPTAN SINGH)

d.

(ASHOK PRASAD)

e.

(SANTOSH RICHHARIYA)

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Followings are the attachment with the application:
- a. Provisional Specification (3 copies)
- b. Drawings (3 copies)
- c. Priority document(s)
- d. Statement and Undertaking on FORM – 3
- e. Power of Authority (Not required)
- f. Fee Rs.**3,000/-** (Rupees Three Thousand only..) in cheque bearing No. dated : drawn on **HDFC Bank Limited, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **14TH** day of **August, 2003.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

FORM 2

The Patents Act, 1970

(39 of 1970)

PROVISIONAL SPECIFICATION

(See Section 10)

AN EFFICIENT PROCESS FOR SELECTIVE PREPARATION OF Z-ISOMER OF CEFDITOREN AND PHARMACEUTICALLY ACCEPTABLE SALTS AND ESTERS THEREOF

RANBAXY LABORATORIES LIMITED

19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a selective process for preparation of Z-isomer of Cefditoren of Formula I as shown in the accompanied drawing and pharmaceutically acceptable salts and esters thereof. Cefditoren possesses a wide spectrum of antibacterial activity against Gram-positive and Gram-negative bacteria.

Cefditoren pivoxil of Formula Ia as shown in the accompanied drawing (also called as ME-1207), which is pivaloxymethyl ester of cefditoren (also called as ME-1206), is a third generation cephalosporin derivative which was first developed by Meiji Seika of Japan with the aim of producing active cephalosporins with potent and broad-spectrum activity (European Patent No 175610). Cefditoren pivoxil is highly active not only against a variety of gram-positive and gram-negative bacteria but also against some resistant strains of bacteria.

Cefditoren pivoxil is chemically [6R-[3(Z),6a,7b(Z)]]-7-[[(2-Amino-4-thiazolyl)(methoxyimino)acetyl] amino]-3-[2-(4-methyl-5-thiazolyl)ethenyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-carboxylic acid, pivaloyloxymethyl ester.

European Patent 175610 describes a process for preparation of Cefditoren and its pharmaceutically acceptable salts and esters. The process described is non-selective and gives more than 20% of unwanted E-isomer which is then separated by means of column chromatography. The yield of cefditoren or its sodium salt or its pivaloxymethyl ester is reported to be very low.

US Patent No 6,288,223 describes a process for the selective preparation of Z-isomer of 3-2 (substituted vinyl)cephalosporins. The process described uses stringent conditions for deprotrotection of the protected amino and carboxyl functionalities. The process isolates every

intermediate followed by its purification and therefore is very time consuming. It gives less yield of Cefditoren pivoxil.

US Patent No 5,616,703 describes a process for separation of cephalosporin isomers by forming amine salts. The process described therein produces the intermediates in which the unwanted E isomer is more than 20% which is then depleted by forming amine salts. In this process the yield of the intermediate reduces and the unwanted E-isomer after separation is thrown out of the process.

Accordingly, the present invention describes an efficient process for the selective preparation of Z-isomer of cefditoren of Formula I or pharmaceutically acceptable salts and esters thereof which solves the drawbacks of the above described methods.

The first aspect of the present invention provides a cost-effective and selective process for the preparation of Cefditoren of Formula I and salts and esters thereof, wherein the required Z-isomer of the Cefditoren and salts and esters thereof are obtained without involving the purification of either the intermediates or the final product for removing the E-isomer.

The second aspect of the present invention provides reaction conditions wherein less than 2% of the Z-isomer is formed during the reaction.

The third aspect of the present invention relates to an enzymatic deacylation of the aminoacyl group present on the 7-position of the cephalosporin nucleus in a neutral to slightly alkaline conditions wherein the hydrolysis of the β-lactam ring is prevented resulting into higher yield of the product having less impurities.

The fourth aspect of the present invention provides a cost-effective and simple three step process for conversion of esters of 7-phenylacetamido-3-chloromethyl-3-cephem-4-carboxylate of Formula II as shown in the accompanied drawing (herein onwards referred to as esters of PCMCC) to Cefditoren pivoxil of Formula Ia which otherwise requires eight steps.

In the first step, esters of PCMCC of Formula II such as p-methoxybenzyl ester of Formula IIa (herein onwards referred to as GCLE) or diphenylmethyl ester of Formula IIb (herein onwards referred to as GCLH) are treated with an alkali or alkaline earth metal iodide or bromide and a phosphorous containing compound of Formula III as shown in the accompanied drawing, wherein Y is absent or oxygen or sulphur, n is an integer 2, 3 or 4 and R is selected from C_1 to C_7 straight or branched chain alkyl, alkenyl, alkynyl or C_6 to C_{10} aryl or aralkyl in an organic solvent to get phosphonium salt of Formula IV as shown in the accompanied drawing which is in-situ reacted with a organic or inorganic base to get a Ylide of Formula V. The Ylide was in-situ treated with 4-methylthiazole-5-carboxaldehyde of Formula VI to get ester of 7-acetamido-3-[(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylate of Formula VII (herein onwards referred to as DPTC). Deprotection of the carboxylic group using a phenol or its ether gave 7-acetamido-3-[(4-methylthiazol-5-yl)vinyl]-3-cephem-4carboxylic acid of Formula VIII (herein onwards referred to as MPTC). MPTC is subjected to enzymatic deacylation reaction at a pH of about 5 to 8 to get an intermediate 7-amino-3-[(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (herein onwards referred to as 7-ATCA) of Formula IX which is isolated as white crystalline solid having less than 2% of E-isomer without carrying out any purification. The overall yield from GCLE to 7-ATCA is 55%. The reaction sequence from GCLE to 7-ATCA was carried out without isolating / purifying any intermediate compounds. However, the isolation and purification of every intermediate is also carried out to ascertain the purity and impurity profile.

In the second step, 7-ATCA is treated with optionally 2-amino protected, activated esters of 2-methoxyimino-2-(2-aminothiazole-4-yl)acetic acid of Formula X as shown in the accompanied drawing, wherein Z is selected from a group having Formula Xa, Xb, Xc, Xd as shown in the accompanied drawing and R_c is monovalent or divalent amino protecting group selected from a group comprising of trityl (triphenylmethyl), acetyl, benzhydryl and acetamidophenyl in presence of an organic solvent and a base to get Cefditoren of Formula I as shown in the accompanied drawing which is converted to its sodium salt of Formula Ib as shown in the accompanied drawing. The sodium salt is isolated as crystals wherein the unwanted E-isomer is less than 1%.

In the third step, sodium salt of Cefditoren acid is treated with halomethyl pivalate of Formula XI as shown in the accompanied drawing wherein the halo group is cholro or bromo or iodo, in an organic solvent to get pharmaceutically acceptable ester of Cefditoren of Formula Ia, which can be optionally purified to get the desired pharmacopoeial purity.

The present invention is described in detail hereunder.

In first step ester of PCMCC of Formula II in step (i) is treated with alkali or alkaline earth metal iodide or bromide and a phosphorous containing compound of Formula III in organic solvent optionally containing water at a temperature of -10 to 50°C. Alkali or alkaline earth metal iodide or bromide can be selected from sodium iodide, potassium iodide, sodium bromide, potassium bromide and such similar metal iodides or bromides. The compound of Formula III wherein Y is absent or oxygen or sulphur, n is an integer 2, 3 or 4 and R is selected from C_1 to C_7 straight or branch chain alkyl, alkenyl, alkynyl or C_6 to C_{10} cycloalkyl, aryl or aralkyl can be selected from trimethylphosphine, triethylphosphine, tributylphosphine, triphenylphosphine, triethylphosphite, triphenylphosphite, triethylorthophosphite or triphenylorthophosphite. Molar ratio of alkali or

alkaline earth metal iodide or bromide and compound of Formula III used is selected in the range of about 0.98 to 1.25 per mole of GCLE. The organic solvent can be selected from a group comprising chlorinated hydrocarbon such as methylene chloride, chloroform, ethylene chloride or ethylene bromide; ethers such as tetrahydrofuran, diisopropyl ether, 1,4-dioxane or diethyl ether; ketones such as acetone, methyl isobutyl ketone, methyl ethyl ketone; lower alcohols such as methanol, ethanol, propanol, isopropanol, butanol or mixtures thereof. Presence of water in the reaction assists the dissolution of metal iodide or bromide. It also makes the reaction biphasic, wherein the inorganic as well as organic side products formed are dissolved and do not actually interfere in the reaction. Quantity of water to be used in the reaction varies from the reaction temperature to moles of reactants and can be 1:0.5 to 1:2 to the quantity of organic solvent. The temperature of the reaction can be between -5 to 50°C. After completion of the reaction, layers can be separated and the organic layer can be used as such for the next step (ii). It is also possible to concentrate the organic layer in vacuum and isolate the product optionally under strict anhydrous conditions.

In step (ii) the organic layer obtained in step (i) or the product isolated after concentration of the said organic layer is treated with a base at a temperature between -20 to 50°C. It is also possible that, the organic layer obtained in step a) i) is cooled to -5 to 10°C and a solution of base in water or suitable organic solvent is added slowly over a period of 15 minutes to 1 hour by maintaining the temperature. The base used in this step can be inorganic compound such as sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, aluminium hydroxide, sodium hydride, potassium hydride, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate or organic salts such as sodium methoxide, potassium t-butoxide, sodium ethoxide, or organic ammonium compounds such as triethylamine, dicyclohexylamine or diphenylamine. For the practical utility a solution of base can be made in a suitable solvent such as water. The strength of such alkali solution can be 0.2 to 1.2 M. The

reaction mass after complete addition of the base is further stirred for about 20 minutes to 1 hour at -5 to 10°C in order to ensure completion of the reaction. After completion of reaction, the organic layer can be separated from the aqueous layer and dried over anhydrous sodium sulphate, magnesium sulphate or a suitable drying agent known to a person skilled in the art. After adjusting the volume of the organic layer with solvent used earlier, it can be used as such in the next step (iii).

In step (iii) to the organic layer obtained in step (ii) which contains a solution of Ylide of Formula V in chlorinated hydrocarbons such as chloroform or methylene chloride is added another organic solvent selected from a group of lower alkanols such as methanol, ethanol, n-propanol, isopropanol and n-butanol; ethers such as tetrahydrofuran, diethyl ether, 1,4-dioxane; esters such as ethyl acetate, n-butyl acetate, isopropyl acetate etc or ketones such as acetone, ethyl methyl ketone etc. Preferably a lower alkanol is used. The ratio of chlorinated hydrocarbon to lower alkanol can vary from 1:1 to 1:0.25. The above said reaction mass containing a mixture of solvents in the said mentioned ratio containing product of step (ii) is cooled to about -50 to -5°C and to it added 4-methylthiazole-5-carboxaldehyde of Formula VI. Reaction mixture is stirred for 15 to 35 hours at –50 to 30°C. After completion of reaction, it is quenched by addition of water followed by washing of organic layer with sodium bisulphite solution to eliminate aldehydic and related impurities generated during Wittig reaction. Organic layer is concentrated under reduced pressure to get a brown coloured residue of DPTC of Formula VII which can be used as such in the next step without any purification or isolation.

DPTC of Formula VII obtained in step (iii) is treated with a phenol or its ether for deprotection of the carboxyl protecting group at a temperature of about 0 to 100°C. A phenol or its ether can be selected from phenol, anisole, 2-cresol, 3-cresol, 4-cresol, resorcinol, catechol, 2-mercaptophenol, 3-mercaptophenol, and 2-methoxyphenol. The reaction can be carried out in

presence of an organic solvent such as lower alkanol, chlorinated hydrocarbon or acetone. However, the reaction can be carried out without using any solvent. When anisole is used for deprotection of the carboxyl protecting group an acid catalyst which can be selected from a group comprising trifluoroacetic acid, formic acid or Lewis acids such as aluminium chloride, boron trifluoride, and anhydrous zinc chloride can be used. After completion of the reaction, n-butyl acetate can be added to the reaction mixture and the organic portion is extracted with sodium bicarbonate solution. The sodium salt of the product gets extracted in the aqueous layer which after separating the layers is washed with n-butyl acetate to remove traces of deprotecting agent. The aqueous layer obtained above can be used as such in the next step without isolating the product, MPTC of Formula VIII.

Deprotection of amino group is a well known art in the field of production and purification of penicillins and cephalosporins. Deprotection mostly involves deacylation for which several references are available (European Patent No. 175610, PCT patent application WO 02/18618, US patent application 20020006642 and US patent application 20020058302). In context to step a) v), investigators persuaded with an objective of deacylating the 7-amino group of the β-lactam ring by employing milder reaction conditions which are not deleterious to the β-lactam nucleus. When enzymatic deacylation of sodium salt of MPTC of Formula VIII was carried out under pH of about 5 to 8 and at a temperature from about 0 to 50°C, it was found that, hydrolysis of the β-lactam ring was negligible and the yield of desired product 7-ATCA of Formula IX was almost quantitative. The reaction can be carried out in water optionally containing an organic solvent which can be miscible or immiscible with water. Such solvent can be selected from lower alkanols such as methanol, ethanol and isopropanol; esters such as ethyl acetate, n-butyl acetate, isopropyl acetate; ethers such as tetrahydrofuran, diethyl ether; chlorinated hydrocarbons such as chloroform, methylene chloride, ethylene chloride and ketones such as acetone. Enzymes suitable for deacylation reactions are for example known as penicillin

acylases or penicillin amidases. These enzymes are classified as E.C. 3.5.1.11. Such enzymes, for example Penicillin G amidase, may be isolated from for example micro-organisms such as fungi and bacteria. The enzyme can be used in immobilized form which can be suitably wet to keep the activity of the enzyme intact. The pH of the reaction mass can be kept in the range of 5 to 8. During this reaction, after deacylation of 7-phenylacetamido group of MPTC, phenyl acetic acid is formed as a by-product which decreases the pH of the reaction mass. In order to maintain the pH between 5 to 8 a base can be added intermittently to the reaction mass. Such a base can be selected from a group comprising of sodium carbonate, sodium bicarbonate, sodium hydroxide, potassium hydroxide, potassium bicarbonate, potassium carbonate or water soluble ammonium compounds such as ammonium hydroxide or triethylamine. The reaction temperature can be kept between 0 to 50°C. After ensuring the completion of the reaction, the enzyme can be filtered and the resultant aqueous filtrate can be acidified with suitable mineral acid such as hydrochloric acid to pH of 3 to 3.5 to affect total precipitation of 7-ATCA of Formula IX at its iso-electric point. Such obtained 7-ATCA of Formula IX almost contains 95% or more of the desired Z-isomer having less than 2% of the undesired E-isomer impurity.

In the second step, 7-ATCA is treated with activated esters of 2-methoxyimino-2-(2-optionally protected aminothiazole-4-yl)acetic acid of Formula X as shown in the accompanied drawing, wherein Z is selected from a group having Formula Xa, Xb, Xc, Xd and R_c is monovalent or divalent amino protecting group selected from a group comprising of trityl (triphenylmethyl), acetyl, benzhydryl or acetamidophenyl as shown in the accompanied drawing, in presence of an organic solvent optionally containing water and using a base at a temperature of about -20 to 60°C to get Cefditoren of Formula I. The activated ester of 2-methoxyimino-2-(2-optionally protected aminothiazole-4-yl)acetic acid of Formula X can be selected from a group comprising of 2-methoxyimino-2-(2-amino thiazol-4-yl)acetic acid, benzotriazol-1-yl ester; 2-methoxyimino-2-(2-amino thiazol-4-yl)acetic acid, S-2-benzothiazole ester (herein onwards

referred as MAEM); 2-methoxyimino-2-(2-amino thiazol-4-yl)acetic acid, dialkylphonate ester or diarylphosphonate ester; 2-methoxyimino-2-(2-amino thiazol-4-yl)acetic acid, dialkylphosphothionate ester or diarylphosphothionate ester. The solvent for this reaction can be selected from a group comprising of chlorinated hydrocarbon such as methylene chloride, chloroform, ethylene chloride or ethylene bromide; ethers such as tetrahydrofuran and diethyl ether; ketones such as acetone, methyl isobutyl ketone and methyl ethyl ketone; alcohols such as methanol, ethanol, propanol, isopropanol and butanol or mixtures thereof optionally containing water. The base used in this step can be inorganic compound such as sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, aluminium hydroxide, sodium hydride, potassium hydride, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate or organic salts such as sodium methoxide, potassium t-butoxide, sodium ethoxide, or organic ammonium compounds such as triethylamine, dicyclohexylamine or diphenylamine. For the purpose of the reaction, the base can be added slowly after preparing a solution of 7-ATCA and MAEM in preferred mixture of solvents. The reaction can be carried out at a temperature of -20 to 60°C. After completion of the reaction, dichloromethane is added to quench the reaction and the layers can be separated. The aqueous layer can be acidified using a suitable mineral acid to adjust the pH between 4.5 to 5. Cefditoren acid of Formula I precipitate out which can be filtered and purified using a suitable solvent or by column chromatography. Alternatively, to the aqueous layer as obtained above can be added acetone and sodium 2-ethylhexanoate at a temperature of about 15 to 30°C to get sodium salt of Cefditoren. The said sodium salt precipitates from the reaction mass as crystalline solid. To complete the crystallization, acetone can be optionally added to the reaction mass and the product can be filtered. The sodium salt of Cefditoren thus obtained has a HPLC purity above 98% wherein the E-isomer as determined by HPLC is less than or equal to 1%. The said crystalline sodium salt has about 6.5 to 7% moisture which suggests that it could be a novel dihydrate of the Cefditoren sodium. In a similar manner using potassium acetate instead of sodium 2-ethylhexanoate,

potassium salt of cefditoren is prepared from cefditoren acid. The potassium salt contains about 6 to 7% intrinsic moisture which suggests that it is in dihydrate form. The salts of cefditoren acid such as calcium, magnesium, zinc, copper, nickel, manganese, rubidium, cobalt, strontium and the like can be prepared using appropriate salt forming agents known to a person skilled in the art. These novel crystalline forms of Cefditoren salts can be very good candidates for development of parenteral dosage form of Cefditoren owing to its high solubility and stability in aqueous conditions.

In the third step, sodium or potassium salt of Cefditoren or Cefditoren acid is dissolved in an organic solvent and reacted with halomethyl pivalate of Formula XI as shown in the accompanied drawing wherein the halo group is chloro or bromo or iodo, at a temperature of about -25 to 35°C. The compound of Formula X can be selected from a group comprising of iodomethyl pivalate, bromomethyl pivalate, chloromethyl pivalate. The organic solvents can be selected from a group comprising dimethylformamide, dimethylacetamide, dimethylsulphoxide, tetrahydrofuran, 1,4-dioxane. The reaction can be carried out at -25 to 35°C. After completion of the reaction, cefditoren pivoxil is obtained by a suitable aqueous work-up followed by extraction with organic solvent. Any organic solvent may be used for extraction which is known to a person of ordinary skill in the art. The solution of cefditoren pivoxil in organic solvent is partially concentrated by evaporation of solvent under vacuum. The product was then precipitated from the said concentrated solution by addition of an anti-solvent selected from a group comprising of n-hexane, diethyl ether, diisopropyl ether, cyclohexane and cycloheptane. The precipitated product is then filtered and can be purified by further crystallization or by column chromatography using hexane-ethyl acetate as eluent.

The intermediate compound 7-ATCA of Formula IX is obtained in good yield and in excellent purity. The content of E-isomer impurity in 7-ATCA of Formula IX according to the process of

present invention is less than 1%. 7-ATCA of Formula IX is a very useful intermediate in synthesis of several cephalosporins. The improved process for preparation of 7-ATCA can be employed in the synthesis of several cephalosporins other than cefditoren or pharmaceutically acceptable salts and esters thereof.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

EXAMPLE 1

PREPARATION OF 7-AMINO-3-[2-(4-METHYL-5-THIAZOLYL)VINYL]-3-CEPHEM-4-CARBOXYLIC ACID (7-ATCA OF FORMULA IX)

To a stirred mixture of GCLE of Formula IIa (10 g, 20.5 mmol) in 60 ml of water and 60 ml of chloroform, was added sodium iodide (3.23 g, 21.5 mmol) and triphenyl phosphine (5.65 g, 21.5 mmol). The heterogeneous mixture was stirred at 25 – 30°C for 3 hrs. The bottom organic layer was separated and cooled to 0 – 5°C. To this 0.40 Molar solution of sodium hydroxide (50 ml) was added at 0–5°C in 20–30 minutes, followed by agitation of 30 minutes at the same temperature. The bottom organic layer was separated and dried over anhydrous sodium sulphate. The volume of the organic layer was adjusted to 120 ml by chloroform. Organic layer containing ylide was cooled to –10 to –15°C and n-propanol (40 ml) was added, followed by addition of 4-methylthiazole-5-carboxaldehyde (8.0 g, 62.9 mmol). Reaction mixture was stirred for 20–24 hours at –10 to –15°C after end of which it was quenched by addition of water (100 ml) followed by washing of organic layer with sodium bisulfite solution. Organic layer was concentrated under reduced pressure to get a brown coloured residue. Phenol (50 ml) was added to the residue to get a clear solution. This solution was stirred at 40–50°C for 10–12 hours and n-

butyl acetate (100 ml) was added to the reaction mass followed by cooling to 5–10°C. Organic portion was extracted with sodium bicarbonate solution (0.17 Molar, 2 x 100 ml). Aqueous layer was washed with n-butyl acetate (2 x 100 ml) to remove traces of phenol. To clear aqueous layer was added Pen-G amidase (5 g wet) at 20–25°C. The pH of reaction was intermittently adjusted to 7.5 to 7.7 by slow addition of 5% sodium carbonate solution. After completion of reaction, enzyme was filtered and washed with DI water. The filtrate was treated with activated carbon and then filtered at 30–35°C. Filtrate was cooled to 20–25°C and to it added dilute HCl (2 Molar) to adjust the pH to 3.0 to 3.5 in order to affect complete precipitation of 7-ATCA. Product was filtered and sequentially washed with water and acetone and finally dried under vacuum to get 3.5 g of off-white title compound in overall yield of 52% from GCLE.

Purity (% Area, by HPLC) : 96.3%

E-isomer impurity (% Area, by HPLC) : 1.87%

^{1}H-NMR (300 MHz, DMSO-d_6) : 2.36 (s, 3H); 3.1 – 3.5 (m, 2H merged with DMSO-peak); 4.81 – 4.83 (d, 1H); 5.05 – 5.07 (d, 1H); 6.31 – 6.35 (d, 1H); 6.65 – 6.69 (d, 1H); 8.91 (s, 1H).

EXAMPLE 2

A) PREPARATION OF CEFDITOREN SODIUM (FORMULA Ib)

A suspension of 7-ATCA of Formula IX (5.0 g, 15.4 mmol) and MAEM of Formula X (6.7 g, 18.6 mmol) in aqueous tetrahydrofurari (60 ml) was stirred at 0 – 5°C. Triethylamine (2.3 ml) was added slowly at 0–5°C over 15–20 minutes. The mixture was stirred at 0–5°C for 2–3 hours. Reaction was quenched by addition of dichloromethane followed by layer separation. Aqueous layer was diluted with acetone to 50 ml. Sodium 2-ethylhexanoate (3.3 g, 19.8 mmol) was added to aqueous acetone solution at 20–25°C. After stirring the mixture for sufficient time for

crystallization of sodium salt of Cefditoren, added acetone (50 ml) slowly to the reaction mass in order to complete crystallization. Filtered the crystallized product under suction and washed with acetone (2 x 10 ml). Product was vacuum dried to get 6.5 g of off-white title compound (Yield = 75%).

Water	:	6.9%
HPLC Purity	:	98%
Z/E ratio (% Area, by HPLC)	:	99 : 1
^{1}H-NMR (300 MHz, D_2O)	:	2.42 (s, 3H); 3.45 (dd, 2H); 4.04 (s, 3H); 5.40 (d, 1H); 5.89 (d, 1H); 6.34 (d, 1H); 6.67 (d, 1H); 7.04 (s, 1H); 8.81 (s, 1H).

B) PREPARATION OF CEFDITOREN POTASSIUM (FORMULA Ic)

A suspension of 7-ATCA (1.0 g, 3.09 mmol) and MAEM (1.34 g, 3.82 mmol) in aqueous tetrahydrofuran (12 ml) was stirred at 0 – 5°C. Triethylamine (0.34 g) in THF (1.0 ml) was added slowly at 0 – 5°C over 15 – 20 min. The mixture was stirred at 0 – 5°C for 2 – 3 hrs. Reaction was quenched by addition of dichloromethane followed by layer separation. Aqueous layer was diluted by acetone to 10 ml. Potassium acetate (0.36 g, 3.67 mmol) was added to aqueous acetone solution at 20 – 25°C. Stirred the reaction mixture for sufficient time to affect crystallization of potassium salt. Added acetone (50 ml) slowly to the reaction mass to complete crystallization. Filtered under suction and washed with acetone (5 ml). Product was vacuum dried to get 1.5 g of off-white product (Yield = 89%).

Water	:	6.54%
HPLC Purity	:	98.1%
Z/E ratio (% Area, by HPLC)	:	99 : 1
^{1}H-NMR (300 MHz, D_2O)	:	2.40 (s, 3H); 3.3 – 3.6 (m, 2H); 4.08 (s, 3H); 5.4 (d, 1H); 5.8 (d, 1H), 6.30 (d, 1H); 6.71 (d, 1H); 7.0 (s, 1H); 8.8 (s, 1H)

EXAMPLE 3

PREPARATION OF CEFDITOREN PIVOXIL (FORMULA Ia)

To a stirred mixture of Cefditoren sodium (20 g) in DMF (120 ml) at –15°C, iodomethyl pivalate (10 g) was added in one lot. Reaction mixture was stirred at –10 to –15°C for 60 min. Subsequently it was quenched by pouring reaction mixture in DI water and ethyl acetate. Ethyl acetate layer was washed sequentially by water, 0.5% $NaHCO_3$ and 0.1% HCl and finally by water. Organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure till residual volume is about 120 ml.

This solution was slowly added to n-hexane (700 ml) at ambient temperature and stir 30 min. The product was filtered under suction and dried under vacuum to get 18.4 g Cefditoren pivoxil.

Yield: 78%

HPLC Purity: 96.8%

E-isomer of Cefditoren pivoxil: 0.78%

Dated **14TH** day of **August, 2003.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited

Application No.

No. of sheets = 11

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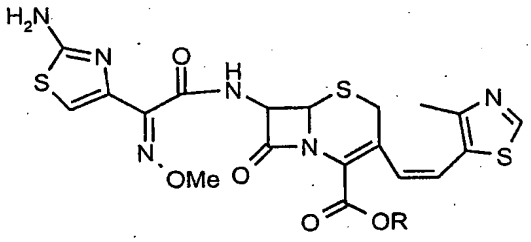
1001-DEL-03

14 AUG 2003

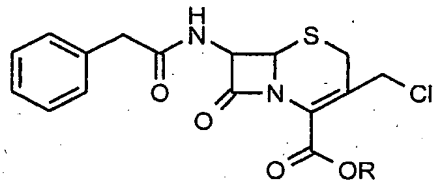


Formula I (R = H)
Formula Ia (R= $(CH_3)_3COOCH_2$-)
Formula Ib (R = Na)
Formula Ic (R = K)

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

1094-DEL-03



Formula II
Formula IIa (R = 4-methoxybenzyl)
Formula IIb (R = diphenylmethyl)

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

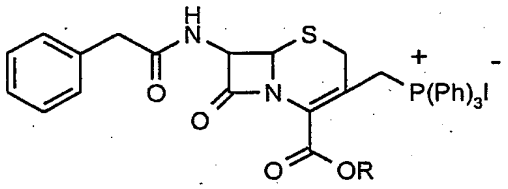
$P(YR)_n$

Formula III

wherein Y is absent or -O- or -S-
n = 2, 3 or 4
R = C_{1-7} alkyl, alkenyl or alkynyl; C_{6-10} aryl, cyclohexyl, aralkyl

For Ranbaxy Laboratories Limited

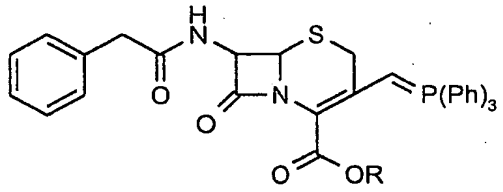
(Sushil Kumar Patawari)
Company Secretary



Formula IV
Formula IVa (R = 4-methoxybenzyl)
Formula IVb (R = diphenylmethyl)

For Ranbaxy Laboratories Limited

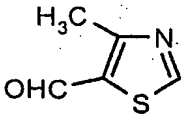
(Sushil Kumar Patawari)
Company Secretary



Formula V
Formula Va (R = 4-methoxybenzyl)
Formula Vb (R = diphenylmethyl)

For Ranbaxy Laboratories Limited

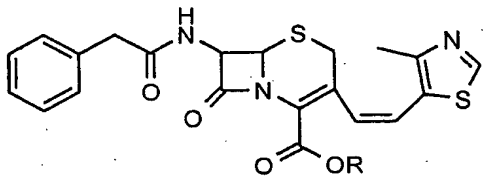
(Sushil Kumar Patawari)
Company Secretary



Formula VI

For Ranbaxy Laboratories Limited

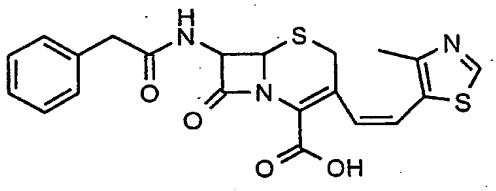
(Sushil Kumar Patawari)
Company Secretary



Formula VII
Formula VIIa (R = 4-methoxybenzyl)
Formula VIIb (R = diphenylmethyl)

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary



Formula VIII

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited

Application No.

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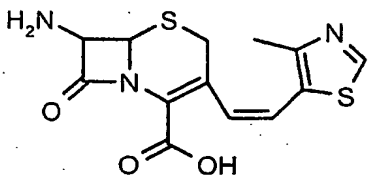


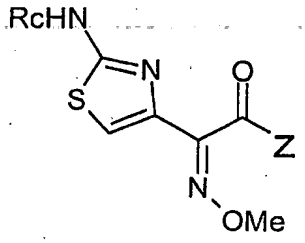
Formula IX

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

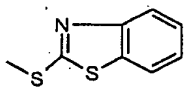
1094-DEL-07

14 AUG 2007

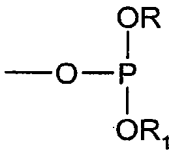


Formula X

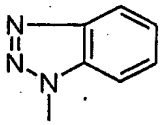
wherein Z is Compound of Formula Xa or Xb or Xc or Xd



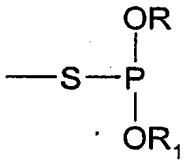
Formula Xa



Formula Xb



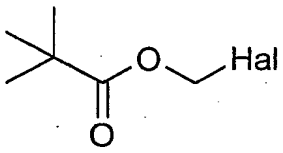
Formula Xc



Formula Xd

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary



Formula XI

wherein Hal = Cl, Br or I

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

ABSTRACT

The present invention relates to an efficient and selective process for preparation of Z-isomer of cefditoren having less than 1% of E-isomer impurity, in three steps from esters of 7-phenylacetamido-3-chloromethyl-3-cephem-4-carboxylate, wherein process for preparation of the intermediate 7-ATCA containing less than 2% of E-isomer impurity, by enzymatic deacylation is also described.